Unusual skin toxicity associated to sustained disease response induced by nivolumab in a patient with non small cell lung cancer

Giulia Galli[1], Claudia Proto[1], Mara Cossa[2], Barbara Valeri[2], Silvana Sdao[3], Diego Signorelli[1], Martina Imbimbo[1], Filippo de Braud[1,4], Marina Chiara Garassino[1], Giuseppe Lo Russo[1]

[1] Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, via G. Venezian 1, 20133 Milan, Italy

[2] Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, via G. Venezian 1, 20133 Milan, Italy

[3] Department of Diagnostic Imaging and Radiation Therapy, Fondazione IRCCS Istituto Nazionale dei Tumori, via G. Venezian 1, 20133 Milan, Italy

[4] Department of Oncology and Hemato-Oncology, University of Milan, via Festa del Perdono 7, 20122 Milan, Italy

Corresponding author:

Giulia Galli, MD

Department of Medical Oncology

Fondazione IRCCS Istituto Nazionale dei Tumori

Via G. Venezian, 1

20133 – Milan, Italy

Phone: +39 02 2390 3108

Fax: +39 02 2390 2775

Mail: giulia.galli@istitutotumori.mi.it

Abstract

Introduction Immunotherapy has shown efficacy in the treatment of different malignancies. Nivolumab, an immune checkpoint inhibitor directed against PD-1, has been approved for Non Small Cell Lung Cancer (NSCLC) in pretreated patients. Although it is generally well tolerated, immunotherapy may be complicated by a wide range of immune-mediated adverse events. Herein we describe the case of an uncommon skin toxicity arising as *alopecia universalis*, induced by nivolumab in a patient with NSCLC.

Case description A 61-year-old man received nivolumab for metastatic NSCLC after progression to 3 lines of chemotherapy. The treatment was prescribed in June 2016, and induced a rapid and significant disease response. Nivolumab was well tolerated until May 2017, when a partial alopecia at hair and eyelashes appeared. In the next months, alopecia became complete and extended to the whole body surface. The dermatologic picture was compatible with *alopecia areata.* A topical steroid therapy was attempted, without benefit. The patient refused systemic treatments and is still undergoing nivolumab, without new toxicities and with persistent disease response.

Conclusions This case suggests that *alopecia areata* may be a rare immune-related adverse event of immune checkpoint agents. Its late onset in our patient is very uncommon and unexpected, underlining that the risk of nivolumab-induced toxicity is not limited to the beginning of treatment. Though its rarity, *alopecia areata* should be considered in the range of adverse events potentially induced by immune checkpoint inhibitors even in the long term. Potential association between toxicity and efficacy of immunotherapy in NSCLC warrants further investigation.

Keywords: alopecia; efficacy; immune checkpoint inhibitor; non small cell lung cancer; toxicity.

Introduction

Immune Checkpoint Inhibitors (ICIs) are a class of anti-cancer drugs that stimulate immune response towards neoplastic cells through different molecular mechanisms. Nivolumab is a fully-human IgG4 monoclonal antibody, which binds Programmed Death-1 (PD-1) expressed on T-lymphocytes. Hence it blocks its interaction with Programmed Death Ligand-1 (PD-L1) physiologically present on antigen-presenting cells, but also on tumor cells. The complex PD-1/PD-L1 has an inhibitory effect on T-lymphocytes and is a crucial mechanism through which tumor cells escape immune surveillance. In recent years, the efficacy of nivolumab has been proved in the treatment of different malignancies, such as melanoma, lung cancer, head and neck cancer.[1] In particular, this drug has been approved for the treatment of metastatic Non Small Cell Lung Cancer (NSCLC) in second or more advanced lines of therapy, irrespective of PD-L1 expression.[2] All ICIs can induce immune-related adverse events (AEs) potentially affecting various organs, with different grades of severity and time of insurgence. Skin toxicity is infrequent and generally limited to pruritus, erythematous rash and less commonly *vitiligo.* The onset of dermatologic AEs is often quite early and their grade of severity is usually mild to moderate.[3] Herein we report a particularly uncommon manifestation of delayed skin toxicity, associated to an exceptional disease response, in a patient with advanced NSCLC receiving nivolumab. We precise that the patient provided written informed consent for the publication of his case.

Case description

EB, a Caucasian male, was born in March 1956 and was a current smoker of 30 pack-year. His medical history was unremarkable and he did not assume any chronic therapy. In December 2014, he was diagnosed with right lung adenocarcinoma extended to mediastinal nodes, with an isolated right cerebellar lesion determining compression of the fourth ventricle. Due to neurologic symptoms, he received radiosurgery (12 Gy in single fraction) soon after diagnosis, with complete neurologic recovery. Then he was treated with two cycles of chemotherapy with cisplatin 75 mg/sm i.v. d1 q21 and pemetrexed 500 mg/sm i.v. d1 q21 from February to March 2015. Due to lung progression at the first disease evaluation, second-line docetaxel 75 mg/sm i.v. d1 q21 was prescribed, but it had to be immediately interrupted because of an infusion reaction with rash and hypotension during the administration of the first cycle. Therefore, the treatment was changed to gemcitabine 1250 mg/sm i.v. d1,8 q21, but after only two cycles further lung and liver progression was documented at Computed Tomography (CT) scan. Moreover, the patient showed a progressive worsening of Performance Status (PS) with dyspnea at rest, cough, severe pain, significant

weight loss and fatigue (Karnofsky PS 50%). In June 2015, as soon as immunotherapy became available at our Center, third-line nivolumab 3 mg/kg i.v. d1 q14 was prescribed, in spite of the worsening of patient's general conditions. Surprisingly, a significant partial response at all extra-encephalic disease sites and brain stability were reported at the first evaluation. Lung and mediastinal lesions underwent further progressive response during the following year, while liver metastases completely disappeared and the brain lesion remained stable (Figure 1).

[insert Figure 1]

In parallel with radiologic response, the patient's conditions showed extraordinary gradual improvement with complete recovery of Karnofsky PS to 100%, in a picture of so-called "Lazarus syndrome" (Table 1). From June 2016 to November 2017, repeated CT and brain magnetic resonance (MRI) scans confirmed disease stability. No AEs related to immunotherapy were reported until May 2017, when the patient firstly noticed partial alopecia at hair and eyelashes. In the following month, alopecia rapidly progressed and became complete, involving all body hair, eyelashes, eyebrows, beard and whiskers (Figure 2). The only concomitant symptom was a mild pruritus without rash, lasting for about one month and then spontaneously resolving. After the disappearance of pruritus, onycolysis with Beau lines and nail pitting appeared (Figure 2).

[Insert Figure 2]

Blood tests to rule out endocrine disorders (e.g. pituitary, adrenal and gonadal hormones) and *sella turcica* MRI were performed, without showing any abnormalities. The patient performed a dermatologic consultation, which diagnosed *alopecia areata* on the basis of physical exam. A diagnostic confirmation was obtained through a skin biopsy of the scalp, showing the typical histological pattern of immune-mediated alopecia (reduced density of deep hair follicles, aspects of intra-follicular malacia, peri- and intra-follicular lympho-monocitic infiltrate with prevalence of $CD4^+$ lymphocytes) (Figure 3).

[Insert Figure 3]

A steroid therapy with oral prednisone 25 mg q.d. was suggested, but the patient refused it, being afraid of toxicity and possible interference with immunotherapy activity. Indeed, the patient was prescribed topic steroid therapy for hair (1% hydrocortisone lotion), which was tried for about two months without any benefits and then interrupted. At the present, EB is still receiving nivolumab. Complete alopecia persists, but the patient's general conditions are still excellent and no new toxicities have been reported.

Conclusions

Alopecia areata is a common dermatologic disease affecting 2-3% of general population. Its most common manifestation is a non-itchy, non-scarring hair loss in one or more sharply defined body areas. A rare and particularly invalidating variant of this condition is *alopecia universalis*, inducing a generalized hair loss extended to the whole body surface. Nail alterations like pitting, dystrophy and Beau lines (i.e. transverse grooves of the nail plate) are frequently associated with the most severe forms of the disease. About one third of the patients with *alopecia areata* undergo spontaneous partial or complete recovery of hair growth from 6 to 12 months from the first manifestations of the disease; however, almost all the affected people develop recurrent alopecia in the next years and the condition tends to become chronic.[4] In the case herein described, we interpreted the development of a rapidly progressing form of *alopecia universalis* as an immune-related AE consequent to nivolumab treatment. Despite the absence of specific features able to differentiate the iatrogenic variant of the disease from the idiopathic one, this hypothesis was based on different considerations. First of all, the age of onset of the alopecia in this patient is not consistent with the typical epidemiology of *alopecia areata*, which makes its first appearance before the age of 40 in 80% of cases and before the age of 20 in 50% of cases. Secondarily, the only predisposing factor for idiopathic *alopecia areata*, in particular for its late-onset forms, is the co-existence of an auto-immune disorder like celiac disease, systemic *lupus erythematosus* and Graves hyperthyroidism.[5] Since our patient does not have either familiar or personal anamnesis of auto-immunity, no predisposing conditions for alopecia can be identified. Thirdly, *alopecia areata* has a known auto-immune pathogenesis, which probably involves the activation of T-lymphocytes against hair follicles as a consequence of aberrant antigen presentation by particular Human Leukocytes Antigen (HLA) alleles.[6] Nivolumab, like all ICIs, is able to induce a wide range of immune-mediated AEs potentially affecting all organs and mimicking the corresponding idiopathic conditions. The pathogenesis of immune-mediated toxicity, based on a hyper-activation of T-lymphocytes which lose the physiologic inhibitory stop and react against self epitopes, is consistent with the underlining mechanism of *alopecia areata.*[7] However, as neither nivolumab discontinuation after the insurgence of the toxicity nor drug rechallenge were made, the most convincing evidence supporting a correlation between a drug and an adverse event cannot be obtained. At the best of our knowledge, there is only a previous work in literature reporting cases of *alopecia areata* during immunotherapy for cancer.[8] Notably, all patients were affected by metastatic melanoma or renal cell carcinoma, so this is the very first case reported in a patient with NSCLC treated with immunotherapy. Moreover, all the 4 cases described developed skin toxicity in concomitance with other systemic adverse events (colitis, transaminitis, itchy rash and elevated hemoglobin, diabetes mellitus). On the contrary, our patient is showing an optimal tolerance to nivolumab and *alopecia*

areata still remains the only reported AE. Another aspect to underline in our case is the very late timing of insurgence of the skin toxicity, which occurred after almost two years of treatment in a state of absolute well-being, while all previously reported cases of alopecia appeared within the first year from the beginning of immunotherapy. In our patient, the delayed toxicity was associated to an early and prolonged response to treatment, with an exceptional clinical benefit. In conclusion, this uncommon case underlines the possibility that a wide range of rare toxicities may develop during therapy with ICIs, with atypical features in relation to timing of insurgence, target organs, or both. Although alopecia in course of IO is very rare, it can be associated to a radical modification of external appearance, with potentially severe psychological distress. Therefore, a concise information about the chance of this uncommon event in occasion of the informed consent may be advisable. Furthermore, the essential diagnostic management of ICI-related alopecia should be standardized, in order to exclude potential underlying etiologies. This overview should include endocrine profile of thyroid, gonadal and adrenal function, and brain MRI with focus on pituitary gland. On the other hand, the possibility that rare and/or severe toxicities may be associated to the efficacy of treatment still remains an open issue and deserves further investigation.[9,10] The comprehension of the pathogenesis of immune-related AEs and the standardization of their management should be optimized in the next future, also in the perspective of the emergence of newer therapeutic strategies whose safety profiles may be partially unknown (e.g. anti-LAG, anti-TIM3, anti-GITR).

Aknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of Conflicting Interests

CP declares travel accommodations and honoraria with MSD International GmbH, BMS, Eli Lilly. DS declares travel accommodations and honoraria with AstraZeneca, MSD International GmbH, BMS. FdB provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom received honoraria or education grants: Amgen, AstraZeneca, Boehringer-Ingelheim, BMS, Eli Lilly, F. Hoffmann-La Roche, Ignyta, Merck Sharp and Dohme, Merck Serono, Novartis, Pfizer. MCG declares personal financial interests with the following organizations: AstraZeneca, MSD International GmbH, BMS, Boehringer Ingelheim Italia S.p.A, Celgene, Eli Lilly, Ignyta, Incyte, Inivata, MedImmune, Novartis, Pfizer, Roche, Takeda; she also declares Institutional financial interests with the following organizations: Eli Lilly, MSD, Pfizer (MISP), AstraZeneca, MSD International GmbH, BMS, Boehringer

Ingelheim Italia S.p.A, Celgene, Ignyta, Incyte, Inivata, MedImmune, Novartis, Pfizer, Roche, Takeda, Tiziana, Foundation Medicine; at the end, she has received research funding from the following organizations: AIRC, AIFA, Italian Moh, TRANSCAN. GLR declares travel accommodations and honoraria with AstraZeneca, MSD International GmbH, BMS, Eli Lilly. All other authors have no relevant conflicts of interest to disclose.

References

1. Wang X, Bao Z, Zhang X, et al. Effectiveness and safety of PD-1/PD-L1 inhibitors in the treatment of solid tumors: a systematic review and meta-analysis. *Oncotarget* 2017; 8(35): 59901-59914.

2. Horn L, Spigel DR, Vokes EE, et al. Nivolumab versus docetaxel in previously treated patients with advanced non–small-cell lung cancer: two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). *J Clin Oncol* 2017; 35(35): 3924-3933.

3. Khoja L, Day D, Wei-Wu Chen T, et al. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann Oncol* 2017; 28(10): 2377-2385.

4. Trüeb RM and Reis Gavazzoni Dias MFRG. Alopecia areata: a comprehensive review of pathogenesis and management. *Clinic Rev Allerg Immunol* 2018; 54(1): 68-87.

5. Barahmani N, Schabath MB and Duvic M. History of atopy or autoimmunity increases risk of alopecia areata. *J Am Acad Dermatol* 2009; 61(4): 581-591.

6. Petukhova L and Christiano AM. Functional interpretation of genome-wide association study evidence in alopecia areata. *J Investigat Dermatol* 2016; 136(1): 314-317.

7. Stucci S, Palmirotta R, Passarelli A, et al. Immune-related adverse events during anticancer immunotherapy: pathogenesis and management. *Oncol Lett* 2017; 14(5): 5671-5680.

8. Zarbo A, Belum VR, Sibaud V, et al. Immune-related alopecia (areata and universalis) in cancer patients receiving immune checkpoint inhibitors. *Br J Dermatol* 2017; 176(6): 1649-1652.

9. Osorio JC, Ni A, Chaft JE, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann Oncol* 2018; 28(3): 583-589.

10. Hasan Ali O, Diem S, Markert E, et al. Characterization of nivolumab-associated skin reactions in patients with metastatic non-small cell lung cancer. *Oncoimmunol* 2016; 5(11): e1231292.

Tables

Table 1. Summary of clinical evolution during treatment with nivolumab.

	Baseline	After 4 cycles	After 8 cycles	After ≥16 cycles
Symptoms/Signs				
Karnofsky PS	50%	70%	90%	100%
Dyspnea	At rest	Light effort	Moderate effort	No
Cough	Yes	Yes	Yes	No
Hemoptysis	Yes	No	No	No
Asthenia[1]	G2	G2	G1	No
Pain[2]	NRS 8	NRS 6	NRS 4	No
O_2 saturation	86% in air	97% in air	99% in air	99% in air
Body weight	68 kg	57 kg	59 kg	78 kg

[1] according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0

[2] according to Numeric Rating Scale for pain (NRS)

Figure Legends

Figure 1. Mediastinal and liver disease response at CT scan from May 2015 to April 2016.

Figure 2. EB's appearance after the development of *alopecia areata* (scalp and nails).

Figure 3. Histology of skin biopsy.